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# CHRONIC MASTITIS: LEADING CAUSE OF UDDER FIBROSIS AND DIFFERENT MEANS OF ITS MANAGEMENT

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## ABSTRACT

Bovine mastitis is an inflammatory response mainly caused by bacteria with substantial economic losses to the world dairy industry and brings issues like food safety for humans. The long-term presence of inflammation of mammary tissue causes chronic mastitis that leads to udder fibrosis. Udder fibrosis is a major problem for dairy cattle, which drops the milk yield. Mastitis at an early stage of lactation results in long-term production loss. In contrast, subclinical mastitis causes an increased risk of getting clinical mastitis in subsequent lactation and premature culling of animals. Risk factors including husbandry practices, milking methods, temperature fluctuation, and irrational use of antibiotics are significantly associated with mastitis. Consequently, the early detection of mastitis is crucial, considering the difficulty of detecting sub-clinical mastitis. So, we can use diagnostic tools such as different chemical tests, ultrasonography, teat endoscopy, and physical examination of the fibrosed udder. It is possible to treat mastitis in early-stage; however, it becomes difficult to treat once the fibrosis occurs. The current manuscript covers a detailed review of published data on mastitis, udder fibrosis causes, manageable factors, and other issues that merit further investigation.

***Keywords*:** Mastitis, Subclinical mastitis, Risk Factors, Udder fibrosis, Mastitis management

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## 1. INTRODUCTION

The most transmissible disease of dairy animals, which affects the quality and quantity of milk produced globally, is mastitis (Balkwill 2004). Mastitis is a dangerous disease of dairy animals and causes massive economic losses (Pal et al. 2019; Du et al. 2022) and occurs repeatedly (Halasa et al. 2007). Chronically infected quarters of the mammary tissue cause lower milk yield (Gonçalves et al. 2020). Mastitis prevalence rate in cow estimate falls within the range of 23.2 and 81.1% for the country (Girma et al. 2012; Zenebe et al. 2014). According to an estimate, an affected quarter suffers 30% reduction in productivity and an affected cow loses 15% of its production for the lactation (Radostits et al. 2007). The economic implication of bovine mastitis is derived from the high costs of diagnosis, treatment, loss of milk production, early culling and cost of the control program in subclinical and

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clinical cases (Khan et al. 2013; Hussain et al. 2013; Qayyum et al. 2016a, 2016b; Ji et al. 2020). Subsequently, the disease has been recognized as one of the major constraints of the dairy sector that needs attention. In recent studies, the work is being done to find the role of the fibroblasts (which were collected from the mastitis infected tissue of the udder of the cow) in the increase of the inflammation and the fibrosis of the mammary tissue (He et al. 2017).

In mastitis, the tissue fibrosis occurred due to too much production of extracellular matrix (ECM) (Zou et al. 2017). Abnormally proliferated fibroblasts, which are activated during mastitis, replace the damaged tissue and produce excessive ECM (Ghosh et al. 2013). Epithelial cells can produce fibroblasts and myofibroblasts by a process named Epithelial-mesenchymal transition (EMT) (Canisso et al. 2021). Epithelial cells undergo the transition to a mesenchymal phenotype to produce these fibroblasts and myofibroblasts (Zou et al. 2017). The main stromal cells of the mammy glands of the bovines are mammary fibroblasts. These fibroblasts control the epithelial cell behavior by cell-to-cell interaction, these interactions may be direct or indirect. Stromal fibroblasts also lead to persistent inflammation of the mammary gland by secreting cytokines, chemokines and growth factors (Buckley 2011; Hasan et al. 2022). Fibroblasts play an important role in changing acute inflammation to adaptive immunity and tissue repair because fibroblasts are the important soldier cells in the immune system (Buckley et al. 2001). The fibroblasts of the diseased tissue show a different type of composition compared with fibroblasts taken from the normal tissue at the same location from the body (Hogaboam et al. 1998; Xu et al. 2007).

Inflammation can stay for a long time when the immune system is overstimulated. The fibroblasts have a long life, and they are present in the inflammation abundantly. Due to their longer life, they can stay in the site of the inflammation for a longer time and may lead to hyperstimulation of the immune system. A control mechanism should be present to avoid the overstimulation of the immune system (Brouty-Boyé et al. 2000; Xu et al. 2007). The molecular basis for the persistently present, activated fibroblasts at sites of chronic inflammation is not yet understood (Buckley et al. 2001). Fig. 1 shows the inflammation of the udder indicating chronic case of mastitis that may leads to the udder fibrosis.

**Fig. 1:** Fibrosed udder after chronic mastitis (left hind quarter teat).

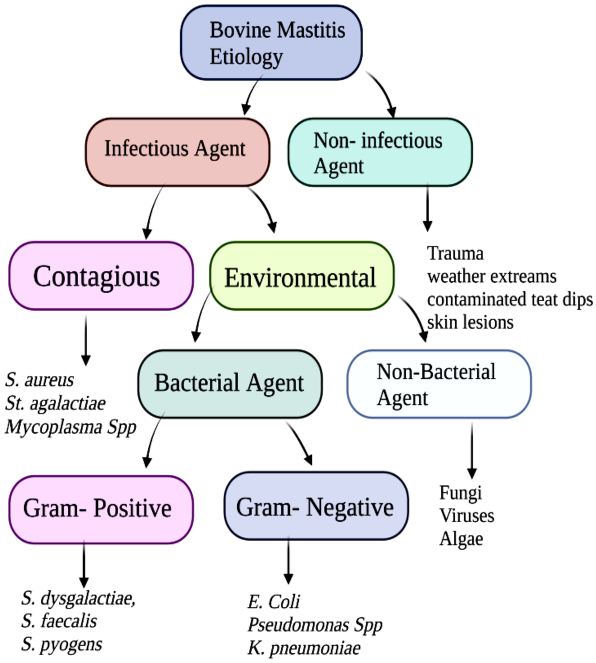


**Fig. 2:** Flow Diagram showing etiology of Bovine Mastitis involving different parameters.

### 1.1. Etiology

The main causative pathogens of the mastitis vary as reported in various studies (Cobirka et al. 2020). Most important pathogen accountable for mastitis in dairy animals is the coagulase-positive Staphylococcus (S.) aureus. Coagulase-negative Staphylococci can also cause clinical or subclinical mastitis (Semik-Gurgul et al. 2021). Even the Gram-positive pathogens are responsible for the severe cases of the mastitis in dairy (Schmenger and Krömker 2020). The 90% of the Staphylococcus species strains isolated from the mastitis-infected animals were S. aureus (Freitas et al. 2018; Du et al. 2022).

Mastitis is caused by a number of the viruses like (Infectious rhinotracheitis, vesicular stomatitis), Bacteria include (*S. aureus*, *Streptococcus* (St.) *agalactia*, *St. dysgalactiae*, *St. faecalis*, *St. pyogens*, *Corynebacterium pyogens*, *St. zooepidemicus*, *Klebsiella species*, *Mycobacterium bovis*, *Escherichia coli*, *Brucella abortus*, *Pseudomonas pyocyaneus*, *Pasteurella maltocida*, *Leptospira Pomona*, *Mycoplasma bovis*, and *Mycoplasma bovigenitalium*), Molds (*Aspergillus fumigatus*), rickettsia, and yeast (Sarma and Hussain 2021).

These all may cause mastitis in different forms i.e. subclinical mastitis caused by the *S. aureus* and the Streptococcus species. Clinical mastitis and per acute mastitis are commonly caused by the *Pseudomonas aeruginosa*, *Escherichia coli*, *S. aureus*, and *St. dysgalactiae*. Acute mastitis is commonly caused by coliform organisms, Subacute mastitis, and chronic mastitis caused by the *St. uberis*, and *S. aureus*. Chronic mastitis lasts long and leads towards the fibrosis of the udder and the affected part of the udder becomes hard which can ultimately lead to the loss of the function of the udder (Sarma and Hussain 2021).

### 1.2. Pathogenesis

*S. aureus* in a persistent infection can cause the chronic form of the mastitis by escaping through macrophage phagocytosis and produces mammary gland fibrosis (Bi et al. 2020). The process of chronic mastitis infection is that the mastitis causing bacteria can live in the host phagocytes and some non-phagocytic cells as well as mammary epithelial cells without being engulfed or phagocytosed; in these cells the antibiotics cannot reach up to the proper concentration failing to trigger innate and acquired immune responses properly. The exact mechanism of the immune responses in the memory tissue is not yet known. There may be chances of immune suppression (Wang et al. 2015).

In mastitis pathogenesis, various cells can generate an immune response like neutrophils (Sladek et al. 2005) macrophages (Sladek et al. 2006) lymphocytes (Sordillo and Streicher 2002) and epithelial cells in the mammary gland (Schukken et al. 2011). A cytokine from the chemokine group is known as a chemoattractant for the lymphocytes called stromal cell-derived factor1(SDF-1), also known as CXCL12 (Kobayashi et al. 2014). In chronic inflammation (as in case of the chronic mastitis), lymphocytes and the dendritic cells are accumulated and stay for a long time at the site of the inflammation because the fibroblasts which are producing the SDF-1, started the overproduction of the SDF-1, which is the chemoattractant for these lymphocytes and the dendritic cells. The SDF-1 (which is secreted by the cancerous fibroblasts) is attached to the receptors (CXCR7 and CXCR4) of these cancerous cells surfaces, and they started to downstream the intracellular signal pathways that control the metastasis, angiogenesis and drug-resistance of these cancer cells (Hattermann et al. 2014). SDF-1 enhanced the breast cancer cells (Kang et al. 2005). SDF-1 also initiates the migration, invasion, survival, proliferation, and adhesion in the cell (Balkwill 2004; Luker and Luker 2006). Even though SDF-1 performs these functions in the cell but still little is known about its role in the start of the EMT and the production of the inflammation in the mammary cells of the bovines.

An experiment found that inflammation-associated fibroblasts (INFs) expressed elevated amounts of vimentin and collagen-1 compared to the normal fibroblasts (NFs). Vimentin is involved in the rigidity of the cells. The skeleton of the collagen-1 can supports the accumulation of the cells like the fibroblast (Oliveira et al. 2010), which in turn produces more and more ECM and other types of the proteins responsible for the fibrosis. Still, INFs expressed a lesser Matrix metalloproteinase-1 (MMP-1) level than NFs. The MMP-1 is involved in the breakdown of the ECM. This MMP-1 is less produced by the INFs and contributes to an increase in the ECM, which can cause fibrosis. Fibroblasts can also secrete cytokines, chemokines and growth factors which can contribute to the persistent inflammation of the mammary glands (Buckley et al. 2001; Shah et al. 2022).

### 1.3. Predisposing Factors to Mastitis Leading Towards Udder Fibrosis

Chilling increases the inflammation of the udder, which is already infected, but this is not proved experimentally. These factors include the feed, age, stage of lactation, teat characteristics, hand and machine milking, and vacuum level (Belay et al. 2022). The rate of udder infection increases with age (Plastridge 1958). Some unknown changes associated with age may be related to susceptibility to St. agalactiae infection (Mvrphy 1947; Lancaster and Stuart 1949). Stage of the lactation also matters, but St. agalactiae infection is not related to the stage of lactation (Plastige et al. 1942). Injuries to teats by stepping the cows to the teat, cuts, lesions, surgeries, can result in the entry of the many kinds of microorganisms inside the mammary tissue, cause inflammation and further aggravate the teat infection (Plastridge 1958). This persistent inflammation can thus lead to fibrosis due to the persistent infection in the mammary tissue (Wang et al. 2015). It is stated earlier that there is an increased prevalence of mastitis in machine-milked animals than in animals milked with using hand. In the latest instances, it is observed that the palms of milker may be a primary source in the spread of udder infections. A vacuum level of over 15 inches of mercury (pressure used in the milking machine) be likely to increase the occurrence of mastitis

(Burkey and Sanders 1949). Fig. 3 depicted various factors associated with bovine mastitis and development of fibrosis in the udder.

### 1.4. Risk Factors

There are many causes of udder fibrosis, but our main concern is mastitis and inflammation related to inflammation. Many factors are responsible for the induction of clinical mastitis i.e., Herd (Schukken et al. 1991; Nyman et al. 2007; Belay et al. 2022) and the factors associated with cow (Barkema et al. 1998; Suriyasathaporn et al. 2000; Riekerink et al. 2007). Among factors associated with cow, somatic cell count is the most important factor in assessing clinical mastitis, with the very low somatic cell count (Suriyasathaporn et al. 2000) and the high somatic cell count (Beaudeau et al. 1998). Heifers have a very low number of clinical mastitis cases except for the

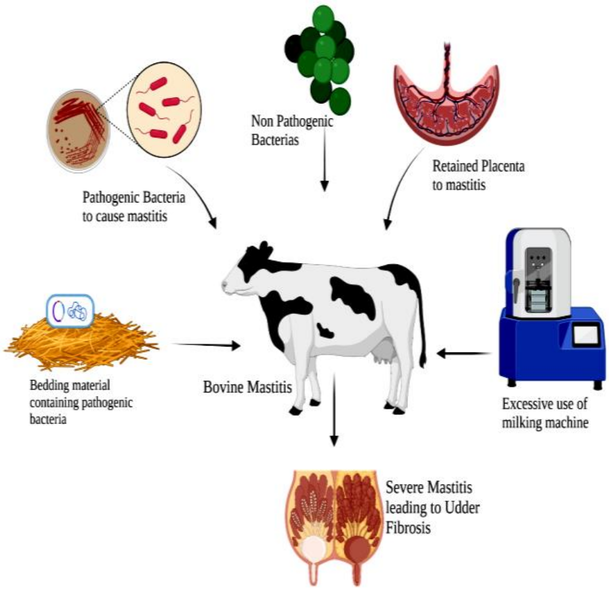


**Fig. 3:** Factors associated with bovine mastitis and udder fibrosis.

**Fig 4:** Affected teats showing swelling, heat, hardness, redness, watery appearance, flakes and pus clots in the milk.

first week of lactation (Barkema et al. 1998; Mohanty et al. 2019). A cow that has clinical mastitis previously will be more prone to clinical mastitis during the next lactation (Houben et al. 1993; Zadoks et al. 2001). Clinical mastitis mostly occurs during the starting days of lactation (Miltenburg et al. 1996). The relationship between the cow-related factors and the pathogen-associated clinical mastitis is not often studied (Zadoks et al. 2001; De Haas et al. 2002; De Haas et al. 2004).

In dairy cattle, genetic variation (for mastitis resistance) is present, generally accepted. The somatic cell count and the clinical causes are the phenotypic traits of mastitis. A genetic correlation exists among these traits; many studies are being carried out to study this type of polygenic variation of the traits. From the economic point of view, consumer concern, welfare, and food safety, it is necessary to add mastitis to the breeding objective of the dairy cattle breeds. Improvements in the selection of the mastitis resistance genetics of the dairy cattle are being studied, and it includes advances in the modeling and udder morphology (Rupp and Boichard 2003).

### 1.5. Diagnosis

Clinical observations or direct or indirect measures of the inflammatory response to infection are the base of the diagnosis of mastitis (Adkins and Middleton 2018). Clinical mastitis may be noticed with the aid of modifications in the appearance of milk, swelling, redness, and elevation in udder temperature. However, animals with subclinical mastitis may be detected most effectively through laboratory tests as subclinical mastitis does not display any gross changes in milk or udder (Reza et al. 2011; Mohanty et al. 2019). Early diagnosis of mastitis is vital because changes in the udder tissue occur much earlier before they become apparent. The prognosis of subclinical mastitis is difficult to interpret as milk seems to be normal physically (Canisso et al. 2021). Numerous strategies are used to diagnose subclinical mastitis, primarily based totally on physical and chemical modifications of milk and isolation of organisms (Batra and McAllister 1984; Emanuelson et al. 1987). The present study indicates that the surf field mastitis test is a very sensitive test that detected the highest number of subclinical mastitis (46%) and clinical mastitis (8%) (Kurjogi and Kaliwal 2014).

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Physical examination of the mammary tissue and the teats is carried out to touch the mammary tissue externally. The consistency is felt by the touch sense., If the consistency feels hard it means there may be fibrosis present. Secondly, there may be the blockage of the teat and the milk that can affect the milk let down, as there are four quarters of the udder and every quarter has a teat attach to it, so the fibrosis may take place in quarter of the udder or may be to all four quarters of the udder. The blockage due to fibrosis may be partial or complete (Pal et al. 2019). Fig. 4 shows affected teat with signs of swelling, heat, hardness, redness, or pain to animals as it was reluctant to touch. That animal's milk had watery appearance, flakes, and clots with pus.

Ultrasonography is used to examine the internal structures of the mammary tissue by using non-invasive techniques. The images are obtained, and thus the internal structures are examined thoroughly, and the type of the injury is determined (Franz et al. 2009). There is another device named, Theloscopy (Teat endoscopy) that is used to visualize the internal structures of the udder and the teat; this technique is very reliable to determine the problems related to the blockage of the teat (Canisso et al. 2021). By this technique, the severity and the degree of the injury to the mammary tissue can be determined (Rathod et al. 2009).

### 1.6. Treatment

Mastitis can lead to fibrosis when not treated. The fibrotic tissue can further proliferate and take the place of the remaining normal soft tissue of the mammary gland (Umadevi et al. 2015). In an experiment, the fibrosed mammary tissue cows were treated with Pendistrin SH intramammary infusion 24 hours for one week and topical massage of Mastilep gel twice a day for 10-15 days. A healing rate of 93% was observed in all the treated cows between 10-15 days (Umadevi et al. 2015).

The formation of fibrous tissue and encircling the pathogen is a shielding mechanism from stopping the propagation of the pathogen. Thus, it considerably hardens the udder and teat cisternae (Nieberle and Cohrs 1966). When fibrous tissue proliferates, either consecutive abscess formation or spontaneous convalescence occurs and literature confirmed no treatment regimen. The infected cow is restrained properly, then fibrosed material from the fibrosed cow udder, teat is crushed by the teat bistoury, and the hand milking removes this material. Then to avoid further adhesion in the teat canals, four plastic tubes are passed through the teat canal (Radostits et al. 2007) followed by the insertion of the intra-mammary tubes for three consecutive days. Antibiotics and anti-inflammatory drugs are also administered. After this treatment, animal shows signs of recovery as the milk comes out of the teat canal both in the amount and quality (Ijaz et al. 2014). The intramammary injection of the Bifidobacterium breve can remove the minor pathogens associated with the mastitis and lower the somatic cell count in the affected quarters of the udder of the dairy cattle. It is the non-antibiotic method to cure chronic subclinical mastitis (Nagahata et al. 2020).

In cases of persistent mastitis, infected mastitis, and neoplastic or hyperplastic conditions of the udder, the radical mastectomy (unilateral or bilateral) is revealed as a recovery process (Andreasen et al. 1993; El-Maghraby 2001; Cable et al. 2004). In many different conditions and persistent suppurative mastitis, pendulous udder, persistent obstructive mastitis, and irreversible udder injuries, mastectomy is specified to remedy inflamed mastitis (Hofmeyr and Oehme 1988). The hemorrhagic complications during a partial mastectomy are very severe because the impacted udder increases in size and is extremely vascularized (Youssef 1999). In affiliation with vascular ligation for mastectomy in cattle, exclusion of the impacted teat has also been described. In cases of chronic mastitis, mastectomy is usually recommended as a pain-relieving technique for enormous lesions involving udder and teat (Cable et al. 2004).

### 1.7. Homeopathic Treatment of Fibrosed Udder

The fibrotic mastitis cows were treated by oral homeopathic remedies like Silicea 200c and Calcarica flour 200c for 20 days, with a recovery rate of 46.45% (Shah et al. 2010). Homeopathic remedies Phellandrium 30c and Carboanimalis 30c were given orally for 21 days to the various cows having differing degrees of udder fibrosis. The recovery rate was 64.28% (Makkar 2017). The clinically chronic fibrosed mastitis cows were treated with the highest recovery rate of 89% by the homeopathic remedies (which are given orally) like Carboanimalis 200c, Silicea 200c and Conium maculatum 200c for 20 days with most of the cows revered in 14.5 days to 27 days (Karthick 2020).

### 1.8. Control and Prevention

Early researchers believe that mastitis management was centered on stopping new infections in healthy cows and decreasing the period of infection (Ruegg 2017). A vaccination schedule should be followed to prevent mastitis in dairy cows. Vaccination should be done with the S. aureus bacterins. Wash the teat and udder with warm water and disinfectant. Dipping the teats before and after the milking helps to control the mastitis. Hygiene should be followed; therefore, wear gloves before the milking. In milking machine farms, the machines should be maintained

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regularly; the vacuum level should be maintained. Cow dry procedures should be followed strictly. The bedding material should be bacteria-free to control the spread of the infection (Sarma and Hussain 2021). To effectively manage chronic clinical mastitis, preventive methods to avoid new infections and the advancement in treatment programs are required (Wente et al. 2020). A very annoying part of clinical mastitis is the recurrent infection (Jamali et al. 2018).

Separate the infected cows from the healthy cows. To prevent the formation of the fibrosis of the mammary tissue due to chronic mastitis, early detection of mastitis is very important (Mimoune et al. 2021). Early detection of mastitis is always helpful for effective control by timely culling the heavily infected cows.

**Conclusion:** Mastitis records high economic losses in the dairy industry. This may be a temporary loss in terms of the decrease in milk production and later recovered from the mastitis and animal's parameters get back to the normal regarding milk. Significant changes were observed in the quality and quantity of the milk. As the pathogenic microorganisms enter the udder, they multiply and deteriorate the anatomy and physiology of the udder. It may lead to a permanent loss in the form of udder fibrosis if the chronic phase persists for a longer time. To avoid chronic clinical mastitis, routine tests for subclinical mastitis detection should be done. By controlling the risk factors and proper pasture management strategies, the ratio of diseased animals can be minimized. Observing the pathway of mastitis pathogenesis and transmission methods, better diagnostic tools can be adopted to lessen the burden of mastitis from the dairy industry.

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